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Predictors of anxiety after stroke: a systematic review of observational studies

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Short Title: A review on predictors of anxiety in stroke

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Abstract

Background: Anxiety disorders or symptoms are relatively common following stroke. A better understanding of the predictors of anxiety in stroke patients may improve the management of these disorders. The current review was conducted to determine the predictors of anxiety following stroke.

Methods: Relevant articles concerning population, hospital or rehabilitation-based studies were identified by searching 10 electronic databases up to May 2014. Methodological quality appraisal, including the validity of prognostic models and data extraction were conducted by three reviewers.

Results: A total of 18 studies were identified. Data from three population-based studies including 8130 patients, 8 hospital-based studies including 1199 patients, and 7 rehabilitation-based studies including 1103 patients was evaluated. Pre-stroke depression, stroke severity, early anxiety and dementia or cognitive impairment following stroke were the main predictors of post stroke anxiety. Older age, physical disability or impairment, and use of antidepressant drugs were not associated with presence of anxiety. Limitations of studies included wide variation in screening tools and cut-off scores, variability in the time frame of screening for anxiety, use of extensive exclusion criteria and questionable statistical internal and external validity of the models.

Conclusions: Lack of methodological and statistical rigour affects the validity of proposed models to predict anxiety after stroke. Future research should focus on testing proposed models on both internal and external samples to ultimately inform future clinical practice.

Introduction

Stroke is a leading cause of mortality and disability worldwide with the number of people diagnosed with stroke rising (1). For survivors, their families or caregivers stroke may constitute a life-changing condition. Many survivors have to cope with significant physical and social consequences. Mental health difficulties such as depression, anxiety, emotional lability and apathy are also common neuropsychiatric outcomes of stroke (2). Approximately 1 in 3 stroke patients develop a mental health disorder after stroke (3.) Unfortunately, the psychological consequences of stroke often remain unrecognised by healthcare professionals, and treatment needs not addressed. In addition, an identified lack of knowledge into the nature of these difficulties often results in poor management of these disorders (4).

Anxiety is a common psychological problem following stroke. The prevalence ranges between 20% within one month following stroke to 24% six months or more after stroke (5). Anxiety disorders or symptoms can also compromise rehabilitation and negatively affect long-term outcomes and quality of life (QoL); thus the significance of patients' psychological status following stroke forms an essential element of their treatment process (6-8).

Although anxiety is common in people who have had a stroke, research in this area is limited (5). Specifically there is no consensus for predictive factors for anxiety after stroke. A better understanding of these might inform management opportunities for this condition and possibly recovery. The current review aims to identify factors predicting anxiety following stroke.

Methods

Our review included studies in populations or groups of patients with a clinical diagnosis of stroke (ischemic or haemorrhagic) who experienced an anxiety disorder or anxiety symptoms. The PRISMA guidelines were followed for the review methodology (9). The methods used for article selection and analysis also sought to be consistent with the methodology of previous benchmark reviews of predictors of depression after stroke (4,10).

Search strategy and selection process

All literature related to anxiety disorders or symptoms in patients with a clinical diagnosis of stroke, was searched. The following electronic databases were used to identify relevant publications: Medline, Pubmed, PsychINFO, PsychArticles, EMBASE, AMED, CINAHL, Proquest Dissertations, Science Direct and EBSCO. The search terms (for title, abstract or keywords) included: Category 1 terms 'stroke' OR 'cerebrovascular disorder' OR 'cerebrovascular accident' AND Category 2 terms 'anxiety' OR 'worry' OR 'fear' OR 'mood disorder' OR 'neurotic disorder' OR 'adjustment disorder'. Searches were restricted to articles that were available (or had an available translation) in English. No constraint was placed on the year of publication. A manual search of the reference lists of selected articles and stroke-related journals was conducted to complement the database search. Eligibility and selection of relevant articles were assessed by screening records based on title/abstract review and by assessing the full text according to predefined inclusion and exclusion criteria. The search, selection process and data extraction was performed independently by two reviewers (LM, RAC). A third reviewer (EC) scrutinized the selection process and cross-checked the data extraction. The PRISMA flow diagram of the search and selection process is outlined in Figure 1.

Criteria for inclusion and exclusion

The following inclusion criteria were used: 1) incidence studies, case control studies or case series that made use of consecutive patient recruitment within clearly defined geographical and time-limited boundaries; 2) studies that used standardised measures to assess anxiety; and, 3) studies that employed regression analyses. Articles were excluded if they: 1) had mixed populations (unless separate results for stroke patients were reported); 2) were limited to select patient characteristics (e.g. age, type of stroke, lesion side); 3) used retrospective recruitment or reporting of mood; or 4) used non-specific measures of psychological distress.

Data extraction and analysis

Diagnostic categories of anxiety included: 1) the presence of an anxiety disorder or anxiety symptoms defined by scores above a cut-off for abnormality on an anxiety scale; 2) severity of an anxiety disorder or anxiety symptoms as defined by scores on an anxiety scale; 3) the presence of a primary anxiety disorder according to any version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (11). Studies were grouped into three categories based on methods of case selection: 1) *population based studies* that attempted to recruit all stroke patients within a certain geographical area (i.e. least biased) (12); 2) *hospital based studies* which included stroke patients from within acute care medical wards in general hospitals; and 3) *rehabilitation based studies* which recruited stroke patients who were either inpatients or attending rehabilitation wards and hospitals, including specialist stroke units.

The analysis within this review focused on multivariate modelling (4), and the quality of multivariate models within selected papers was assessed by extracting data using the criteria detailed by Counsel & Dennis (2001) (12). These criteria include: 1) *external validity* (generalisation of the model), 2) *internal validity* (bias within the model), 3) *statistical validity* (number of events per variable), 4) *evaluation* of the model (quality of the predictions), and 5) *usability or practicality* of the model. For all criteria specific questions were applied. In order to determine external validity, the population the model was generated from (e.g. community or hospital based) and use of major exclusion criteria (e.g. age, type of stroke) were examined. To determine internal validity we evaluated whether outcomes were assessed at appropriate fixed time points, and if all potentially important predictors were entered in the model. Statistical validity was assessed by examining if the number of cases were sufficient for the number of variables included in the model (events per ratio), if collinearity was measured, and if a stepwise analysis was employed. Evaluation of the model was achieved by assessing if the model was validated in data used to generate the model (i.e. the same patient population-internal validation) and/or on populations not used to generate the model (new patients in a separately collected population-external validation); practicality was determined by assessing

whether data required to make predictions were easily available (i.e. sufficient reporting), whether the actual model and coding of variables were described, and if confidence intervals were reported (12).

Results

A search from inception up to May 2014 produced a total of 659 unique references. All titles and abstracts were screened and 77 publications were retrieved for full text review, of which 18 (13-30) met the inclusion criteria (Fig. 1).

Table 1 displays the details of the selected publications. Three population-based studies including 8130 patients, 8 hospital-based studies including 1199 patients, and 7 rehabilitation-based studies including 1103 patients investigated potential factors predictive of anxiety following stroke. The majority of studies (78%) evaluated the prevalence of anxiety and a few assessed the severity of anxiety (4/18) (14,15,20,24). The most common stroke type included was ischemic (67%; 12/18). Five studies did not clearly state which stroke subtype was included (13-17). Twelve studies excluded patients with communication difficulties, cognitive impairment or dementia. Age and gender details were provided for almost all (94%) studies; one study lacked this information (18). Age ranged from 20 to 93 years with a mean age of 66.7 years (based on a total of 6287 patients of the 15 studies adequately reporting age). Three studies assessed for anxiety ≤7 days post stroke (16,19,20) and 10 studies assessed patients at least 30 days post stroke (13,15-17,19-24). The longest follow-up period was 10 years (16).

In the multivariate models study samples at baseline ranged from 19 (25) to 2179 (16) patients. A total of seven different measures were used to assess anxiety and/or the severity of anxiety symptoms in the samples (Table 2). Only three studies used more than one diagnostic instrument to measure anxiety (14,15,22), most studies (78%) used only one measure, including a clinical structured interview (26) based on the DSM criteria (11). The Hospital Anxiety and Depression Scale (HADS), a 14-item scale with 7 items used to screen for anxiety symptoms was the most frequently employed

diagnostic screening measure (11/18) followed by the Posttraumatic Diagnostic Scale (PDS; 3/18), and the Hamilton Anxiety and Depression Scale (HAM-A; 3/18) (31-33). DSM criteria using information from structured interviews was only used in two studies (22,26). Different cut-off points were used to establish the presence of anxiety. Of the studies that utilised the HADS to measure anxiety, one used a cut-off score of ≥5 for the partial scores and ≥10 for the total scores (27), three used a cut-off of >7 (16,17,19), three used a cut-off of >8 (18,22,28), one used >11 (29) and three did not report cut-off scores (13-15). Ghika-Schmid et al. (1999) (21) used a cut-off of 6-11 to indicate minor anxiety and >14 for major anxiety on the HAM-A, and Kroeders et al. (2013) (25) used 6-8 for borderline anxiety and ≥9 for morbid anxiety on the Irritability Depression and Anxiety scale (34). Barker-Collo et al. (2007) (30) employed the Beck Anxiety Inventory (35) and used the following cut off points, 0-7 for minimal anxiety, 8-15 for mild anxiety, 16-25 for moderate anxiety and 26-63 for severe anxiety. Of the two studies that used the PDS, severity of anxiety utilised cut-off scores of mild 1-10, moderate 11-20, moderate to severe 21-35 and severe ≥36 (14,15). Four studies did not report any on the cut-offs used to measure anxiety (13,20,23,24).

Table 1 summarises the quality of analyses employed by the 18 studies. The external validity varied between studies and only three studies showed good external validation (21,25,29). The majority of studies (14/18) had employed several exclusion criteria, (e.g. communication difficulties, cognitive impairment or dementia) which may have limited the generalizability of the results. Only one study did not report age and gender (18). There was little variation in relation to internal validity across the studies. Four studies included an adequate number of patients of the inception cohort in their follow-up (16,18,23,25,30). However, in two of these studies the follow-up assessment was conducted in the acute phase (i.e. < 30 days) (18,25). Only three studies completed a baseline assessment within seven days following stroke (16,19,20), and fixed time periods were only employed in eight studies (13,16,17,19,22-24,28). Although some studies included sex and age, previous history of anxiety was not examined suggesting the quality of analyses to be poor across all studies. As these have been

theoretically associated with anxiety, the quality of the models could have been improved by including all of the variables instead of some or none (36).

The statistical quality also varied across the studies. Given our inclusion criteria, all identified studies used regression as this allows a better exploration of the relationship between variables assessed than correlation analyses. Stepwise analysis was used in 5/18 studies (13,19,23,26,28), which is deemed to be a good test for determining the quality of predictors (37). Studies were evaluated in terms of events per ratio sufficiency, collinearity plus internal and external validity. The models used in eight studies have been deemed to be unstable as their events per ratio were not sufficient (i.e. did not include enough cases in their model) so they were unable to show goodness of fit. The ten studies which did have a sufficient events per ratio accounted for between 11% and 54% of the variance in the presence of anxiety, and between 24% and 58% of the variance in the severity of anxiety. When looking at the relationship among the independent variables assessed in the studies, it is important to note whether collinearity is assessed (i.e. multicollinearity does not contribute to a good regression model); only seven of the 18 studies reported collinearity (14,15,17,18,22,28,30). In line with this, problems with multicollinearity are reduced in stepwise analyses (12) however, only nine studies adopted this method of analysis. Model validation was reported in only one study (29). No studies validated their data with a different population setting (external validation), limiting the generalisability of the findings. Only six studies reported confidence intervals for the predictive probabilities restricting the usability of the studies overall (18,19,22,26,27,29).

Table 3 describes the variables investigated to be predictive of post stroke anxiety. A total of 44 different variables were assessed across the 18 studies, and 33 variables were found to be associated with post stroke anxiety. Main predictive variables were previous (or history of) depression (3/3), early anxiety (i.e. in the acute/intermediate phase after diagnosis) (4/4), stroke severity (2/3), and dementia or cognitive impairment (2/3). However, most variables were examined in one study, and only seven variables (16%) were assessed in ≥ 4 studies. Of these, poor/no association with anxiety

was observed for older age (0/4), physical disability/ADL (2/6), physical impairment (1/4) and use of antidepressants (1/6). Other factors not predicting post stroke anxiety included: a previous history of anxiety, hypertension, diabetes, dissociation, perceptions of control over recovery, recovery confidence, low satisfaction with treatment, physical inactivity, motor function, apathy and incontinence. The majority of studies which included stroke feature variables found consistent associations with the presence of anxiety: left hemisphere (1/1), right hemisphere (2/2), white matter hyperintensity (1/1), network rest functional connectivity (1/1), time since stroke occurred (2/2) and use of anxiolytic drugs (1/1).

Discussion

The purpose of this review was to identify variables predictive of post stroke anxiety. Although a wide range of variables were considered across the 18 studies included in this review, only pre-stroke depression, stroke severity, early anxiety, and an outcome of dementia or cognitive impairment were consistently associated with post stroke anxiety. These factors are in line with wider literature. Anxiety is commonly observed in individuals with cognitive decline or dementias, and depression and anxiety are often found to be co-morbid (5,38,39). The most consistent factor not predictive of post stroke anxiety was older age. This may in part be due to a combination of anxiety disorders being much less common in older adults and an increased risk of large proportion of stroke in those over the age of 65 (40,41).

The results of the current review should be interpreted with caution as most variables were tested in single studies only and the majority of studies showed methodological limitations. Only 2 studies accounted for >50% of the total variation in anxiety symptom burden, but neither were developed with samples large enough to be reliable or validated in another population. The external validity of the models was also reduced: the majority of studies had several exclusion criteria (limiting the ability to generalise findings to the wider stroke population), and were hospital based and not a true representation of all stroke patients in the community. In addition, most of the models were

explanatory (evaluating the relationship of predictive variables to presence and/or severity of anxiety) rather than predictive (examining the probability that anxiety will occur) and therefore limit the use in identifying those patients at high risk of anxiety prior to discharge.

Post stroke anxiety was screened at a range of different time points after stroke, with only three out of 18 studies assessing anxiety during the acute phase of stroke (i.e. within 7 days). Clinical guidelines suggest that stroke patients should be routinely screened for mood disorders within six weeks following the event and those with certain 'risk profiles' could be targeted for screening when resources to screen all patients are not available (42). However, this systematic review clearly showed that there is a lack of understanding or consensus about this screening process. A wide range of measures were utilised to assess anxiety; some were based on DSM criteria, others focused on specific anxiety disorders (i.e. PDS) or omitted somatic symptoms (i.e. HADS). However, the majority of studies used only one measure (mainly screenings tools), and often employed measures that were not validated for different age groups or in a stroke population (43,44). This led to a mixture of anxiety symptoms being explored and limits the validity in anxiety screening as it overlooks the apparent differences in anxiety between younger and older people, or in those with different presentations. In these respects there is hope for the future, the Geriatric Anxiety Inventory (45), a simple binary response instrument designed particularly for older adults is currently subject to trial in an older stroke sample (46). The GAI's response format also supports its use in individuals with mild cognitive impairment (47). In addition, a newly developed observational measure, the Behavioural Outcomes of Anxiety Scale (48,49) offers promise for assessment of those with aphasia after stroke. Routine use of the new DSM 5 criteria (11), where practicable, might also assist.

Our results also revealed a wide variation in the use of cut-off scores on measurement instruments, even when the same screening tool (i.e. HADS) was applied; this could have contributed further to the inconsistencies in the presence of anxiety and symptom severity in the samples. It identifies an urgent need for structured guidance on screening tool use and for validation of anxiety screening measures in the stroke populations (5). In particular as a recent review into the specificity/sensitivity

and clinical utility of mood screening tools in stroke patients revealed that only 7/27 identified screening tools were used to assess anxiety, of which only the HADS was able to identify anxiety accurately however with a mixed clinical utility (50).

A recommended focus for future research would be the applications of the models identified in this review. Specifically, the focus should be on clinical practice to assess predictability, quality, and the effect on patient outcomes (12). Moreover, research methodologies should be standardised: use of standard agreed measures, cut-offs, samples, time points of assessments and methods of data analysis which will contribute to enhanced understanding and treatment of post stroke anxiety. This will also enable better comparability between studies and clearer associations of predictors of post stroke anxiety. Last, our review excluded TIA patients and was limited to patients with actual stroke events. TIA is considered a precursor to stroke and has previously been defined as a brief episode (< 24 hours) of focal loss of brain function (51, 52). However, data shows that the number of patients diagnosed with a TIA is increasing (53) and it may therefore be pertinent to identify predictors of post anxiety in this population in future studies.

With focus of research shifting towards likely characteristics and predictors of post stroke anxiety, targeted interventions can be developed to reduce anxiety. There has been evidence to suggest that social support systems (e.g. religious communities) may act as a protective factor and that involving individual's networks more closely in the rehabilitation approach may be beneficial (27). Moreover, cognitive rehabilitation should be routinely implemented into standard rehabilitation as this review demonstrated that it is associated with post stroke anxiety.

In conclusion, the present models of anxiety and stroke present some concern. A lack of rigour may have impacted on the validity of the predictor variables identified. Further recommendations for future research suggest that the models should be both internally, but most importantly externally

validated to help develop guidelines and inform health care practice to improve outcomes after stroke.

Conflicts of interest

None declared

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Table 1. Quality of multivariate modelling in studies of anxiety following stroke

	Population			*Hospital-based*								*Rehabilitation-based*						
Criteria	**Ayerbe - 2014**	**Broomfield – 2013**	**Leppavuori.- 2002**	**Castellanos-Pinedo - 2011**	**Fure - 2006**	**Ghika-Schmid - 1999**	**Kim - 2011**	**Kroeders - 2013**	**Lassalle-Lagadec - 2012**	**Morrison - 2005**	**Tang - 2012**	**Barker-Collo - 2007**	**Field - 2008**	**Giaquinto - 2007**	**Lincoln - 2013**	**Merriman - 2007**	**Sagen - 2010**	**Wang - 2011**
Study details																		
Time of Assessment	3m, 1y annual to 10y	NR	3- 4m	4 - 26w	3-7d	4d-3m	1w-3m	< 2w	10d -3m	10d -3y	3m	3m	?-3m	<3w	2,4,6m,5y	1m-1y	2w-4m	1-3m
Proportion of Anxiety (%)	34 (3m)	32	21	34	26	29	56	53	–	–	6	21	–	42	29 (5 y)	30	23	30
Total number of cases in model	2179	3831	277	83	178	31	131	19	24	40	693	73	70	132	532	102	104	90
Predicting presence of anxiety	√	√	√	√	√	√	√	√	-	√	√	√	-	-	√	√	√	-
Predicting severity of anxiety	-	-	-	-	-	-	-	-	√	-	-	-	√	-	-	√	-	√
Stroke subtypes																		
Ischemic	-	-	√	√	√	√	√	√	√	-	√	√	-	√	-	-	√	√
Intracerebral haemorrhage	-	-	-	-	-	-	-	√	-	-	-	√	-	√	-	-	√	√
Subarachnoid haemorrhage	-	√	-	-	-	√	-	-	-	-	-	√	-	-	-	-	√	√
Undetermined	√	-	-	-	-	-	-	-	-	√	-	-	√	-	√	√	-	-
External validity																		
No major exclusion criteria	-	√	-	-	-	√	-	√	-	-	-	-	-	-	-	-	-	-
Age details of population provided	√	√	√	√	-	√	√	√	√	√	√	√	√	√	√	√	√	√
Sex details of population provided	√	√	√	√	-	√	√	√	√	√	√	√	√	√	√	√	√	√
Internal validity																		
Inception cohort																		
Assessed ≤ 7d post stroke[a]	√	-	-	-	-	-	√	-	√	-	-	-	-	-	-	-	-	-
< 10% cohort excluded or lost at follow-up	-	-	-	√	√	-	-	√	-	-	-	√	-	-	-	-	-	-
Timing of outcomes																		
Fixed time points for assessment	√	-	-	√	-	-	√	-	-	√	√	-	-	-	√	-	√	√
>30 d follow up	√	-	-	√	-	√	√	-	√	√	-	-	√	-	√	-	√	√
Important predictors in multivariate model																		
Age	√	√	-	√			√		√		√	√		√	√		√	
Sex	√	√	-	√					√	√	√	√		√	√		√	
Previous anxiety	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 1 continued																	
Statistical validity																	
Regression analysis performed	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Events per ratio sufficient[b]	√	√	√	√	√	-	-	-	-	-	√	-	-	√	√	-	√	√
Stepwise analysis	-	-	√	√	-	-	√	-	-	√	√	-	-	-	-	-	-	-
Collinearity assessed	-	-	-	-	√	-	-	-	-	-	√	√	√	-	√	√	√	-
Model Evaluation																	
Internal validation (% predicted)	-	83.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
External validation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Practicality of model																	
Feasible predictor variables	-	√	√	-	√	-	-	√	-	-	√	√	√	-	-	√	√	-
Actual model given	√	√	-	-	√	-	√	√	-	-	√	√	√	√	√	√	-	√
Variance presence anxiety (%)	-	11	-	-	-	-	-	-	-	-	-	51	-	-	16	54	-	-
Variance severity anxiety (%)	-	-	-	-	-	-	-	-	-	-	-	-	24	-	-	58	-	34
Confidence intervals given	-	√	√	-	√	-	√	-	-	-	-	-	-	√	-	-	√	-

Abbreviations: NR = not reported; d=day; w=week; m=month; y=year;

[a] Studies in which patients were seen within one week of stroke onset were defined as having the most adequate inception cohort (11).

[b] Ratios considered sufficient if there were at least 20 persons for each independent variable included in a linear regression model or at least 10 outcomes for each independent variable included in a logistic regression or proportional hazards model (54).

Table 2. Summary for measures used to assess anxiety

Measure	Administration	No. items; scale	No. of studies utilised measure
HADS[a]	Self-report	7[a]; 4-point	11 studies (13-19, 22, 27-29)
PDS	Self-report	17; 4-point	3 studies (14, 15, 24)
HAM-A	Interviewer administered, self-report	14;	3 studies (20, 21, 23)
DSM criteria	Interviewer administered	NA	2 studies (22, 26)
BAI	Self-report	21; 4-point	1 study (30)
IDA	Self-report	18; 4-point	1 study (25)
PTCI	Self-report	33; 7-point	1 study (15)

NA, not applicable

HADS = Hospital Anxiety and Depression Scale (31); PDS = Posttraumatic Diagnostic Scale (32); HAM-A = Hamilton Anxiety Rating Scale (33); DSM = Diagnostic and Statistical Manual of Mental Disorders (11); BAI = Beck Anxiety Inventory (34); IDA = Irritability Depression Anxiety Scale (35); PTCI = Posttraumatic Cognitions Inventory (55).

[a] Only the anxiety sub-scale was incorporated in the review.

Table 3. Variables predictive of anxiety following stroke associated anxiety.

	Population			*Hospital-based*								*Rehabilitation-based*							
	Ayerbe, 2014	***Broomfield, 2013***	***Leppavuori, 2002***	***Castellanos-Pinedo, 2011***	***Fure, 2006***	***Ghika-Schmid, 1999***	***Kim, 2011***	***Kroeders, 2013***	***Lassalle-Lagadec, 2012***	***Morrison, 2005***	***Tang, 2012***	***Barker-Collo, 2007***	***Field, 2008***	***Giaquinto, 2007***	***Lincoln, 2013***	***Merriman, 2007***	***Sagen, 2010***	***Wang 2011***	***Total***
Demographic																			
Age: Older	-	-	-		-	-	X	-	-	-		X	-	-	X	-	X	-	0/4
Younger	-	√√	-	√√	-	-	-	-	-	-	X	-	-	-	X	-	-	-	3/5
Education	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0/1
Sex: Female	√√	√√	-		-	-	-	-	-	√√	X	X	-	-	X	-	-	-	3/6
Male	-	-	-	√√	-	-	-	-	-	-	-	-	-	-	X	-	-	-	1/2
Social (baseline)																			
Living Alone	-	-	-	-	√√	-	-	-	-	-	-	-	-	-	-	-	X	-	1/2
Socioeconomic deprivation	-	√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1
Medical history (pre-stroke)																			
Vascular Risk Factors	-	-	-	X	-	-	√√	-	-	-	-	-	-	-	-	-	-	-	1/2
Previous Stroke	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	√√	-	-	1/2
Hypertension	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	0/1
Smoking	√√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1
Diabetes	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	0/1
Epilepsy	-	-	√√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1
Insomnia	-	-	√√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1
Cognitive Status	-	-	-	-	-	-	-	-	-	-	-	√√	-	-	-	-	-	-	1/1
Anxiety	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0/1
Depression	-	-	√√	√	-	-	-	√√	-	-	-	-	-	-	-	-	-	-	3/3
Unable to Work	√√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1

Table 3 continued																			
Stroke features (acute)																			
Hemisphere: Left	-	-	-	-	-	-	-	-	-	-	-	√√	-	-	-	-	-	-	1/1
Right	-	-	-	√√	-	-	-	-	-	-	√√	-	-	-	-	-	-	-	2/2
White matter hyperconnectivity	-	-	-	-	-	-	√√	-		-	-	-	-	-	-	-	-	-	1/1
Network rest functional connectivity	-	-	-	-	-	-	-	-	√	-	-	-	-	-	-	-	-	-	1/1
Disability / ADL	√√	-	-	-	X	-	-	-	-	X	-	-	-	-	X	-	X	√	2/6
Stroke severity[a]	√√	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	√	2/3
Time since stroke	-	-	-	-	-	-	-	-	-	-	-	-	-	-	√√	√√	-	-	2/2
Use anxiolytic drugs	-	-	√√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1
Outcome features																			
Alexithymia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	√	1/1
Dementia / cognitive impairment	X	-	-	√√	√	-	-	-	-	-	-	-	-	-	-	-	-	-	2/3
Physical impairment	-	-	-	-	X	-	√	-	-	-	-	X	-	-	-	-	X	-	1/4
Use antidepressants	X	-	√√	-	-	-	-	-	-	-	X	-	X	-	-	X	X	-	1/6
Early anxiety	-	-	-	√	-	-	-	-	-	√√	-	-	√√	-	-	-	√√	-	4/4
Apathy	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	0/1
Migraine frequency	-	-	√√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1
Incontinence	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0/1
Paresis	√√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1
Motor function	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	0/1
Other																			
Physical inactivity	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	0/1
QoL: Mental	√√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/1
Physical	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0/1
Treatment centre[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	√√	-	-	-	1/1
Low satisfaction with treatment	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	0/1
Recovery confidence	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	0/1
Negative affect	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	√√	-	-	1/1
Perceptions of control over recovery	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	0/1
Cognitive appraisals	-	-	-	-	-	-	-	-	-	-	-	√√	-	-	√√	-	-		2/2
Dissociation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-		0/1
Behavioural denial of stroke	-	-	-	-	-	√	-	-	-	-	-	-	-	-	-	-	-		1/1
Spirituality / religious beliefs	-	-	-	-	-	-	-	-	-	-	-	-	√	-	-	-	-		1/1

Table 3 continued

√√ = Variable significant in multivariate analysis;

√ = Variable only significant in univariate analysis;

X = Variable not significant in univariate modelling

No symbol indicates that variable was not assessed

Abbreviations: QoL = quality of life.

[a] Glasgow score < 9

[b] Participants were recruited from rehabilitation centres in Belgium, UK, Switzerland and Germany.